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TITLE: Comparison of the Long-Term Efficacy of Tissue-Engineered Vascular Grafts Versus Polytetrafluoroethylene Conduits Using an Established Preclinical Model

PRINCIPAL INVESTIGATOR: Christopher Breuer, MD

CONTRACTING ORGANIZATION: Research Institute at Nationwide Children's Hospital

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Comparison of the Long-Term Efficacy of Tissue-Engineered Vascular Grafts Versus Polytetrafluoroethylene Conduits Using an Established Preclinical Model

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6. AUTHOR(S)
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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
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Columbus, OH 43205-2664

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

The long-term goal of this ongoing project is to utilize a regenerative medicine approach to develop improved biomaterials designed specifically for use in infants and children requiring congenital heart surgery. All currently available prosthetic biomaterials suffer from adverse events arising from poor biocompatibility.[6] In contradistinction to prosthetic biomaterials, use of autologous tissue significantly reduces the risk of these complications.[7] Thus the use of autologous tissue represents the best option for performing a major reconstructive cardiac operation when treating pediatric patients with congenital heart disease due to the reduced risk of complications and the growth capacity of autologous tissue.[7] Regrettably, there is rarely sufficient autologous tissue to enable performance of a major congenital heart surgery without the use of prosthetic biomaterials, therefore; prosthetic biomaterials are used in the vast majority of congenital heart surgeries.[7] Furthermore, because of the continuing lack of improved biomaterials, many medical and surgical strategies have been developed over the years to compensate for and enable the use of the suboptimal patches, grafts, and valves. For example, anticoagulation therapy is often used to reduce the risk of thromboembolic events, while surgeons frequently use oversized prostheses or delay surgical procedures until a child achieves a predefined weight in order to reduce the risk of somatic overgrowth.[8-10] These strategies are effective and necessary to enable congenital heart disease patients to undergo life-saving operations, but they are maladaptive and come at a cost. Anticoagulation significantly increases the risk of bleeding complications; while use of oversized grafts disrupts laminar flow which increases the risk of thromboembolic complications.[8-10] Delaying surgery exposes the patient to prolonged chronic hypoxia which has adverse developmental consequences in addition to exposing the heart to prolonged volume overload which increases the risk of heart failure.[9] Thus these strategies add to the procedure-related morbidity and mortality however, due to the lack of an alternative (i.e., a conduit with growth capacity) these risks are simply assumed and deemed unavoidable.

15. SUBJECT TERMS

NONE LISTED

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
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a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**	UU	**22**	**19b. TELEPHONE NUMBER** *(include area code)*
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1. INTRODUCTION:

In this study we will use an established large animal model (the ovine IVC vascular interposition graft model) to evaluate the late-term performance of the second generation TEVG versus the PTFE graft. Data from these studies will be used to supplement data from our ongoing clinical trial and are necessary for obtaining regulatory approval for the TEVG using the orphan regulatory pathway. Successful completion of this work would enable the widespread use of the first vascular graft with growth capacity which could be used to prevent somatic overgrowth, a critical problem in the field of congenital heart surgery.

2. KEYWORDS:

ectopic calcification, mechanobiology, inflammation, scaffold, polytetrafluoroethylene

3. ACCOMPLISHMENTS:

What were the major goals of the project?

The long-term goal of this ongoing project is to utilize a regenerative medicine approach to develop improved biomaterials designed specifically for use in infants and children requiring congenital heart surgery. All currently available prosthetic biomaterials suffer from adverse events arising from poor biocompatibility.[6] In contradistinction to prosthetic biomaterials, use of autologous tissue significantly reduces the risk of these complications.[7] Thus the use of autologous tissue represents the best option for performing a major reconstructive cardiac operation when treating pediatric patients with congenital heart disease due to the reduced risk of complications and the growth capacity of autologous tissue.[7] Regrettably, there is rarely sufficient autologous tissue to enable performance of a major congenital heart surgery without the use of prosthetic biomaterials, therefore; prosthetic biomaterials are used in the vast majority of congenital heart surgeries.[7] Furthermore, because of the continuing lack of improved biomaterials, many medical and surgical strategies have been developed over the years to compensate for and enable the use of the suboptimal patches, grafts, and valves. For example, anticoagulation therapy is often used to reduce the risk of thromboembolic events, while surgeons frequently use oversized prostheses or delay surgical procedures until a child achieves a predefined weight in order to reduce the risk of somatic overgrowth.[8-10] These strategies are effective and necessary to enable congenital heart disease patients to undergo life-saving operations, but they are maladaptive and come at a cost. Anticoagulation significantly increases the risk of bleeding complications; while use of oversized grafts disrupts laminar flow which increases the risk of thromboembolic complications.[8-10] Delaying surgery exposes the patient to prolonged chronic hypoxia which has adverse developmental consequences in addition to exposing the heart to prolonged volume overload which increases the risk of heart failure.[9] Thus these strategies add to the procedure-related morbidity and mortality however, due to the lack of an alternative (i.e., a conduit with growth capacity) these risks are simply assumed and deemed unavoidable.

What was accomplished under these goals?

Specific Aim 1: Determine the degree of ectopic calcification and compare results between TEVGs and PTFE grafts	**Timeline**	**Status**
Major Task 1	Months	
Subtask 1: Submit documents for ACURO approval	1-4	Completed 1/18/2022
Milestone: ACURO approval obtained	6	Completed 4/25/2022
Subtask 1: Initiate CT study evaluating and comparing the degree of ectopic calcification between TEVG and PTFE grafts.	7	Completed in 1/4/2022
Milestone: Perform first non-contrast CT	7	Completed in 1/4/2022
Subtask 2: Complete assessment of ectopic calcification using CT	7-19	Completed in 7/7/2022
*Milestone**:** Perform non-contrast CT scans on 100% of all surviving (TEVGs N=14) and (PTFE grafts N=9) animals*	19	Completed in 10/20/2022
Specific Aim 2 Determine the degree of ectopic calcification and compare results between TEVGs and PTFE grafts		
Major Task 2		
Subtask 1: Initiate in vivo compliance testing studies	13	Completed 1/4/2023
Milestone: Perform first in vivo compliance testing catheterization	13	Completed 1/4/2023
Subtask 2: Complete in vivo compliance assessment	13-24	Completed 5/8/2023
*Milestone**:** Perform in vivo compliance catheterizations on 100% of surviving (TEVGs N=14) and (PTFE grafts N=9) animals*	24	Completed 5/8/2023
Subtask 3: Initiate in vivo vasoreactivity testing study	25	In Process for 2024
Milestone: Perform first in vivo vasoreactivity catheterization	25	In Process for 2024
Subtask 4: Complete in vivo vasoreactivity assessment	25-36	In Process for 2024
Milestone: Perform in vivo vasoreactivity assessment on 100% of surviving (TEVGs N=14) and (PTFE grafts N=9) animals	36	In Process for 2024

Specific Aim 3 Evaluate and compare the hemodynamic performance of TEVGs and PTFE grafts at rest and during physiological stress		
Major Task 3		
Subtask 1: Initiate MRI studies	37	In Process for 2025
Milestone: Perform first MRI	37	In Process for 2025
Subtask 2: Complete MRI studies including computational fluid dynamics and simulations	37-47	In Process for 2025
Milestone: Complete performance of MRI studies including computational fluid dynamics and simulations on 100% of all surviving (TEVGs N=14) and (PTFE grafts N=9) animals	48	In Process for 2025
Subtask 3: Prepare HDE supplement reviewing findings of Preclinical study	48	Dr. Breuer/ Dr. Shinoka
Milestone: Submit HDE supplement to FDA	48	

What opportunities for training and professional development has the project provided?

We have established “Individual Development Plans” for each student and post-doc, which guide us in mentoring these talented young people through their projects. In addition, lab members participate fully in our group lab meetings with both our large and small animal study teams. Finally, we participate in quarterly Tissue Engineering and Modeling (TEAM) Conferences which rotate between Nationwide Children’s Hospital, Yale University, Cornell University, and Stanford University. We find these face-to-face meetings essential for performing multidisciplinary translational research.

How were the results disseminated to communities of interest?

Dissemination of results will primarily be by peer reviewed publication. Our first paper has been recently submitted.

In the next reporting period, we plan to perform the vasoreactivity studies on our 14 TEVG and 9 PTFE animals, along with the comprehensive data analysis. We estimate to this to be complete in the fall of 2024.

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

With completion of the analysis of our CT data, it indicates that our TEVGs are resistant to the ectopic calcification seen with the clinical standard GoreTex grafts. This has potential to impact what materials are used in the clinic to repair congenital heart defects.

What was the impact on other disciplines?

Nothing to Report

What was the impact on technology transfer?

Nothing to Report

What was the impact on society beyond science and technology?

Nothing to Report

5. CHANGES/PROBLEMS:

No changes or problems during this period.

Actual or anticipated problems or delays and actions or plans to resolve them

No changes or problems during this period

Changes that had a significant impact on expenditures

Not Applicable

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Significant changes in use or care of human subjects

No human subjects are used in this study.

Significant changes in use of biohazards and/or select agents.

Nothing to report

6. PRODUCTS:

- **Publications, conference papers, and presentations**

- **Journal publications.**

Our manuscript "Tissue Engineered Vascular Grafts Are Resistant to the Formation of Dystrophic Calcification" (reference number: NCOMMS-23-49801-T) was recently submitted to Nature Communications.

Books or other non-periodical, one-time publications.

Nothing to report

Other publications, conference papers and presentations.

Data generated from this grant was presented at The World Congress of Congenital Heart Defects by Dr. Christopher Breuer, in Washington DC, August of 2023.

- **Website(s) or other Internet site(s)**

Nothing to report

- **Technologies or techniques**

Nothing to report

- **Inventions, patent applications, and/or licenses**

Nothing to report

- **Other Products**

Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name: Christopher Breuer, MD
Project Role: PD/PI
Researcher Identifier (eRA Commons): cbreuer
Nearest person month worked: 1.8 calendar months
Contribution to Project: Oversees all aspects of the project.

Name: Toshiharu Shinoka, MD
Project Role: Co-Investigator
Researcher Identifier (eRA Commons):
Nearest person month worked: 0.84 calendar months
Contribution to Project: Leads catheterization and angiography procedures.

Name: Mitchel Stacy, PhD
Project Role: Co-Investigator
Researcher Identifier (eRA Commons):
Nearest person month worked: 3.0 calendar months
Contribution to Project: Leads CT procedures and image analysis.

Name: Jennifer Cooper, PhD
Project Role: Co-Investigator
Researcher Identifier (eRA Commons): JNNJOROGE
Nearest person month worked: 0.25 calendar months
Contribution to Project: Consults on experiments and results

Name: Thomas West
Project Role: Project Manager
Researcher Identifier (eRA Commons): aaron5
Nearest person month worked: 2.16 calendar months
Contribution to Project: Assists with catheterization procedures and organization of the sheep study

Name: Eric Heuer
Project Role: Research Associate
Researcher Identifier (eRA Commons):
Nearest person month worked: 6.0 calendar months
Contribution to Project: Assists with catheterization procedures

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Dr. Christopher Breuer

ACTIVE

Other Support – Project/Proposal
ACTIVE
Title: Improving Tissue Engineered Vascular Graft Performance via Computational Modeling
Major Goals: Developing a novel computational model to predict the natural history of TEVG development, including its possible transient narrowing, and to direct the clinical use of angioplasty.
Status of Support: Active
Project Number: R01HL139796
Name of PD/PI: Breuer, C., Humphrey, J., Marsden, A.
Source of Support: National Institutes of Health /NHLBI
Primary Place of Performance: Research Institute Nationwide Children's Hospital
Project/Proposal Start and End Date: (MM/YYYY: 04/20/2022-03/31/2026
Total Award Amount (including Indirect Costs):
Person Months (Calendar/Academic/Summer) per budget period.
Year (YYYY) Person Months (##.##)

3. 2024 1.2 calendar
4. 2025 1.2 calendar

Title: Preservation and Rescue of the Lung Donor Allograft for Transplantation
Major Goals: The goal of this study is to evaluate the role of MG53 on lung donor allograft organ preservation using a mouse lung transplantation model.
Status of Support: Active
Project Number: R01HL143000
Name of PD/PI: Whitson, B.
Source of Support: The Ohio State University/NIH/NIAID
Primary Place of Performance: Research Institute Nationwide Children's Hospital
Project/Proposal Start and End Date: (MM/YYYY) (if available): 09/30/2018-06/30/2023
Total Award Amount (including Indirect Costs):
Person Months (Calendar/Academic/Summer) per budget period.
Year (YYYY) Person Months (##.##)

2. 2023 0.12 calendar

*Title: Development and preclinical validation of an improved tissue engineered vascular graft for use in congenital heart surgery

*Major Goals: Research on tissue engineering approaches to patches, grafts, and transplantation
that provide structural support, restore native activity, allow for tissue growth, and prevent the need for reoperation.

*Status of Support: Active
*Project Number: W81XWH1810518
*Name of PD/PI: Breuer, C.
*Source of Support: Department of Defense
*Primary Place of Performance: Research Institute at Nationwide Children's Hospital
*Project/Proposal Start and End Date: (MM/YYYY) (if available): 09/30/2018-09/29/2023
*Total Award Amount (including Indirect Costs):
*Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY) Person Months (##.##)
1. 2023 0.54 calendar

*Title: Investigating Novel Cellular Therapies to Prevent and Treat Acute Antibody Mediated Kidney Transplant Rejection

*Major Goals: Provide mouse kidney transplant model establishment and applies the mouse kidney transplant model to investigate cellular therapies and to prevent and treat acute antibody
mediated kidney transplant rejection.

*Status of Support: Active
*Project Number: R01AI139913
*Name of PD/PI: Bumgardner. G.
*Source of Support: The Ohio State University/NIH/NIAID
*Primary Place of Performance: Research Institute at Nationwide Children's Hospital Project/
Proposal Start and End Date: (MM/YYYY) (if available): 07/01/2019-12/31/2023
*Total Award Amount (including Indirect Costs):
*Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY) Person Months (##.##)
2. 2023 0.12 calendar
3. 2024 0.12 calendar

*Title: Preservation of Donation after Cardiac Death Allograft Integrity for Liver Transplantation
*Major Goals: Overall, the long-term goal of this project centers on testing the hypothesis that "muscle-liver crosstalk, via MG53 as a myokine, constitutes a physiological component of hepatocellular protection by membrane-delimited interaction with MLKL and intracellular action
on cell survival signaling". We envision that rhMG53 can function as a novel biological reagent
to improve donor organ preservation and function during liver transplantation.
*Status of Support: Active
*Project Number: R01DK123475
*Name of PD/PI: Black, S.
*Source of Support: The Ohio State University /National Institutes of Health
*Primary Place of Performance: Research Institute at Nationwide Children's Hospital
*Project/Proposal Start and End Date: (MM/YYYY) (if available): 06/15/2020-11/30/2023
* Total Award Amount (including Indirect Costs):

* Person Months (Calendar/Academic/Summer) per budget
period.

Year (YYYY) Person Months (##.##)
2. 2023 0.12 calendar
3. 2024 0.12 calendar

*Title A Study Evaluating the Safety and Efficacy of Second-Generation Tissue Engineered Vascular Grafts (TEVG-2)
*Major Goals: This grant supports funding for the control arm a TEVG2, a clinical trial ev aluating the use of tissue engineered vascular grafts on congenital heart surgery.
*Status of Support: Active
*Project Number: NA
*Name of PD/PI: Galantowicz, M.
*Source of Support: Gunze Limited
*Primary Place of Performance: Research Institute at Nationwide Children's Hospital
*Project/Proposal Start and End Date: (MM/YYYY) (if available): 06/01/2020-05/31/2023
*Total Award Amount (including Indirect Costs):
*Person Months (Calendar/Academic/Summer) per budget period.
Year (YYYY) Person Months (##.##)
2. 2023 0.12 calendar

*Title: A Study Evaluating the Safety and Efficacy of Second-Generation Tissue Engineered Vascular Grafts
*Major Goals: In this study, we will evaluate the short-term (2 year) safety and efficacy of a second-generation TEVG for use as an extracardiac conduit in children with single ventricle cardiac anomalies undergoing modified Fontan surgery.
*Status of Support: Active
*Project Number: UH3HL148693
*Name of PD/PI: Breuer, C.
*Source of Support: National Institutes of Health /NHLBI
*Primary Place of Performance: Research Institute at Nationwide Children's Hospital
*Project/Proposal Start and End Date: (MM/YYYY) (if available): 03/01/2021-02/28/2025
*Total Award Amount (including Indirect Costs):
*Person Months (Calendar/Academic/Summer) per budget period.
Year (YYYY) Person Months (##.##)
2. 2023 3.0 calendar
3. 2024 3.0 calendar
4. 2025 3.0 calendar

*Title: Establishment of Large Animal Model for Investigating Cardiopulmonary Remodeling after Fontan Surgery
*Major Goals: The overarching goal of this proposal is to develop a computational model that can describe and predict cardiopulmonary remodeling that results from hemodynamic perturbations of Fontan surgery using an experimental-computational approach. Central to this
study is development of a Fontan survival animal model. We will use data generated using this
model to inform, develop, and validate a "multiscale fluid-solid-growth" (mFSG) computational
model that can aid in understanding cardiopulmonary remodeling, assessing potential modifications of the surgical approach, and designing regenerative medicine interventions.
*Status of Support: Active
*Project Number: NA
*Name of PD/PI: Breuer, C.

*Source of Support: Additional Ventures
*Primary Place of Performance: Research Institute at Nationwide Children's Hospital
*Project/Proposal Start and End Date: (MM/YYYY) (if available): 02/02/2021-12/31/2022
*Total Award Amount (including Indirect Costs):
*Person Months (Calendar/Academic/Summer) per budget period.
Year (YYYY) Person Months (##.##)
1. 2023 0.6 calendar

*Title: Elucidating the Molecular Mechanisms Underlying Lyst Mediated Tissues Engineered V ascular Graft Stenosis
*Major Goals: The ability of LYST modulation to inhibit the formation of TEVG stenosis without adversely impacting neovessel formation exceeds all other approaches we have developed to date. Our overriding hypothesis is that modulation of LYST-mediated neotissue formation can be used to inhibit the formation of TEVG stenosis and enable the development of a cell-free TEVG. Aim 1: Evaluate the temporal factors critical to the formation of LYST mediated TEVG stenosis. Aim 2: Determine the role of macrophages on the formation of LYST mediated TEVG stenosis. Aim 3: Investigate the role of macrophage-derived extracellular vesicles (EVs) on intercellular signaling and the formation of LYST-mediated stenosis.
*Status of Support: Active
*Project Number: 1 R01HL157491-01
*Name of PD/PI: Breuer, C.
*Source of Support: National Institutes of Health
*Primary Place of Performance: Research Institute at Nationwide Children's Hospital
*Project/Proposal Start and End Date: (MM/YYYY) (if available): 04/1/2021-03/31/2025
*Total Award Amount (including Indirect Costs):
*Person Months (Calendar/Academic/Summer) per budget period.
Year (YYYY) Person Months (##.##)

2. 2023 1.2 calendar
Year (YYYY) Person Months (##.##)
3. 2024 1.2 calendar
4. 2025 1.2 calendar

*Title: Preclinical Evaluation of Tissue Engineered Human Acellular Vessels
*Major Goals: Initial preclinical evaluation of the use of the Tissue engineered vessel as a Blaylock-Tussig Shunt in a non-human primate model
*Status of Support: Active
*Project Number: NA
*Name of PD/PI: Breuer, C.
*Source of Support: Humacyte Inc.
*Primary Place of Performance: Research Institute Nationwide Children's Hospital
*Project/Proposal Start and End Date: (MM/YYYY) (if available): 04/01/2019-06/30/2023
*Total Award Amount (including Indirect Costs):
*Person Months (Calendar/Academic/Summer) per budget period.
Year (YYYY) Person Months (##.##)
1. 2023 0.12 calendar

*Title: Pulmonary Artery Patch Reconstruction Preclinical Study
*Major Goals: Preclinical evaluation of the safety and efficacy of a tissue engineered patch used for pulmonary artery augmentation in an ovine model.

*Status of Support: Active
*Project Number: NA
*Name of PD/PI: Breuer, C.
*Source of Support: University of Zurich
*Primary Place of Performance: Research Institute at Nationwide Children's Hospital
*Project/Proposal Start and End Date: (MM/YYYY) (if available): 02/03/2022-05/31/2023
*Total Award Amount (including Indirect Costs):
*Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY) Person Months (##.##)
1. 2023 0.06 calendar

*Title: Cell-free vascular grafts: Immunological response and vascular regeneration
*Major Goals: The primary objective of this study is to explore the mechanism through which VEGF modulates the inflammatory response, employ novel transgenic mouse models to monitor monocyte infiltration into the grafts and study the role of VEGF signaling on inflammation and graft regeneration and explore the long-term patency and remodeling of A-TEV in a large, preclinical animal model (ovine) to assess the clinical potential of these grafts.
*Status of Support: Active
*Project Number: R01HL151196
*Name of PD/PI: Andreadis, S.
*Source of Support: Research Foundation for SUNY on behalf of University of Buffalo/NIH
*Primary Place of Performance: Research Institute at Nationwide Children's Hospital
*Project/Proposal Start and End Date: (MM/YYYY) (if available): 04/10/2020-03/31/2023
*Total Award Amount (including Indirect Costs):
*Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY) Person Months (##.##)

2. 2023 0.12 calendar

*Title: Cardiomyocyte Patch Validation Study
*Major Goals: Evaluate the efficacy of the Procardian patch to maintain cardiac output using a murine LAD ligation model.
*Status of Support: Active
*Project Number: NA
*Name of PD/PI: Breuer, C.
*Source of Support: Procardian
*Primary Place of Performance: Research Institute at Nationwide Children's Hospital
*Project/Proposal Start and End Date: (MM/YYYY) (if available): 01/04/2023-01/03/2024
*Total Award Amount (including Indirect Costs):
*Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY) Person Months (##.##)
2023 .06 cal months

*Title: Comparison of the long-term efficacy of tissue engineered vascular grafts versus polytetrafluoroethylene conduits using an established preclinical model
*Major Goals: In this study we will use an established large animal model (the ovine IVC vascular interposition graft model) to evaluate the late-term performance of the second generation TEVG versus the PTFE graft. Data from these studies will be used to supplement data from our ongoing clinical trial and are necessary for obtaining regulatory approval for the TEVG using the orphan regulatory pathway. Successful completion of this work would enable the widespread use of the first vascular graft with growth capacity which could be used to prevent somatic overgrowth, a critical problem in the field of congenital heart surgery.

*Status of Support: Active
*Project Number: W81XWH2210597
*Name of PD/PI: Breuer, C.
*Source of Support: Department of Defense
*Primary Place of Performance: Research Institute at Nationwide Children's Hospital
*Project/Proposal Start and End Date: (MM/YYYY) (if available):
09/30/2022-09/29/2026
*Total Award Amount (including Indirect Costs):
*Person Months (Calendar/Academic/Summer) per budget period.
Year (YYYY) Person Months (##.##)

2. 2023 1.8 Calendar
3. 2024 1.8 Calendar
4. 2025 1.8 Calendar
5. 2026 1.8 Calendar

What other organizations were involved as partners?

Nothing to report

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: ***N/A***

QUAD CHARTS: *N/A*

9. APPENDICES: *N/A*